REMARKS

The last Office Action of August 26, 2010 has been carefully considered. Reconsideration of the instant application in view of the foregoing amendments and the following remarks is respectfully requested.

Claims 1-23 are pending in the application. Claims 20-23 have been withdrawn from further consideration. Applicant herewith affirms the withdrawal of claims 20-23 from further consideration. Claims 1 and 14 have been amended. Claims 3 and 19-23 have been canceled. No claims have been added. A total of 17 claims is now on file. No amendment to the specification has been made. No fee is due.

Claims 1-7 and 9-19 stand rejected under 35 U.S.C. §103(a) as being unpatentable over WO2004/001915 to Wang et al. ("Wang") in view of U.S. Pat. Publ. No. 2005/0084851 to Ronaghi ("Ronaghi").

Claim 8 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Wang in view of Ronaghi and further in view of U.S. Pat. Publ. 2003/0082537 to Stanton ("Stanton").

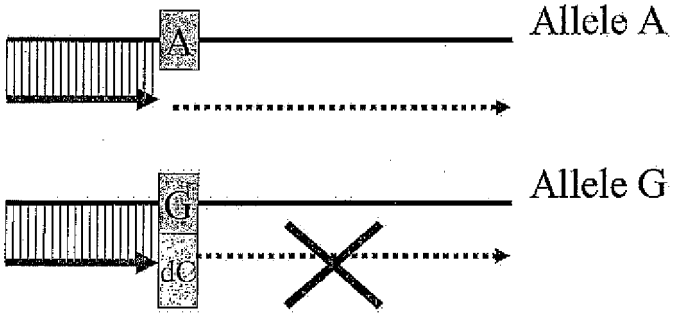
REJECTION OF CLAIMS 1-7 AND 9-19 UNDER 35 U.S.C. §103(a) AS BEING UNPATENTABLE OVER WANG IN VIEW OF RONAGHI

In view of the Examiner's grounds for rejection, applicant has amended original claim 1 to include the limitations of claim 3.

In addition, applicant has also amended claim 14 to include the limitations of claim 3. Claims 3 and 19 have been cancelled.

Amended claim 1 of the present application is directed to a method for determining a target nucleic acid sequence in the presence of a related non-target nucleic acid sequence, wherein a sequencing primer is used which binds to a region of common sequence present on the target nucleic acid as well as on the non-target nucleic acid. With respect to the target nucleic acid, the

sequencing reaction proceeds into two downstream regions of dissimilar sequence between the target and the non-target nucleic acid. The sequencing reaction on the non-target nucleic acid, however, is blocked by sequence-specific incorporation of a terminator nucleotide in the first region of dissimilar sequence. Due to this blocking step, only the sequencing reaction on the target nucleic acid proceeds into the second region of dissimilar sequence.



Using the method according to the present application, it is possible to assign the specific sequences of several regions of dissimilar sequence to one particular target nucleic acid in the presence of one or more related non-target nucleic acids.

The Examiner now cites Wang in combination with Ronaghi as rendering claim 1, claim 14 and others, obvious. In particular, the Examiner cites Example 3 in Wang which is directed to multiplex sequencing of four different single nucleotide polymorphisms simultaneously in the same tube. Applicant contends that the claims 1 and 14, as amended patentably distinguish over the cited references.

In Example 3 of Wang, four different sequencing primers are used each specifically binding to a pair of oligonucleotides which differ from each other in only one nucleotide position near the 5`-end of the primer's target sequence. The sequencing reaction that is performed terminates for each primer at the position of the different nucleotide. Thus, the method described in example 3 of Wang is specifically designed to detect *one particular nucleotide difference*, e.g. one

particular SNP. Therefore, Example 3 is not in the least directed to assigning the actual sequence of several SNPs or other regions of dissimilar sequence to one specific nucleic acid of a pool of different, but related nucleic acids as claimed here. The principle that two consecutive regions of dissimilar sequence of one nucleic acid are analyzed while the sequencing reaction on related non-target nucleic acids is prevented from proceeding cannot be derived from Example 3.

Furthermore, Example 3 in Wang is only directed to the determination of whether a specific SNP, in two otherwise similar nucleic acids, has the same or a different sequence in said two nucleic acids. Determining the sequence of two consecutive SNPs and, in particular, *simultaneously assigning said sequences to one or the other nucleic acid* is not considered in Example 3.

The Examiner points to page 21, line 22 to page 22, line 2 to explain that if a template were used having the same primer regions but lacking the region complementary to the blocker, then amplification lacking the blocker would proceed beyond the blocked site to allow distinguishing between two templates with the same primer region but varying in putative blocking regions. This, according to page 22, lines 3-8 would be "....the basis for use in genotyping by blocking sequencing of one allotype differing from another allotype by only a short insertion to which the blocker could be directed." Thus, Wang teaches blocking the sequencing reaction on a non-target nucleic acid while the sequencing reaction on the target nucleic acid is not blocked. Hereby, however it is necessary to include a short insertion into the non-target nucleic acid for blocking the sequencing reaction. In contrast to this, in the method of the present invention, *no insertion is needed*, but only a single nucleotide polymorphism in the nucleic acid suffices for blocking the sequencing reaction.

Moreover, Wang does not disclose any details of this blocking of the sequencing reaction; specifically, it is not described whether the blocker inhibits annealing of the sequencing primer or elongation during the sequencing reaction. Also, the chemical nature of the blocker is nowhere described.

Accordingly, claims 1 and 14 and the claims dependent thereof teach a completely different aspect than found in the Wang reference. Wang therefore does not provide any motivation or suggestion to the person skilled in the art to carry out the methods claimed by applicant.

The Examiner has further conceded that Wang does not teach that target and non-target sequences have a second region of dissimilar sequence downstream from the corresponding first region of dissimilar sequence, wherein the second region of dissimilar sequence comprises a single nucleotide, or wherein the target and non-target sequences each have a second region of common sequence which lies between the first and second regions of dissimilar sequence, or wherein the target nucleic acid sequence and the non-target nucleic acid sequence comprise one or more further regions of dissimilar sequence downstream of the second region of dissimilar sequence.

However, the Examiner cites Ronaghi as providing these missing elements. Applicant disagrees with the Examiner because Ronaghi teaches a fingerprinting method that has nothing to do with the limitations recited by the Examiner as missing in Wang, and the Examiner does not specifically point out, where in the Ronaghi reference the missing elements and steps are found. Ronaghi teaches more of a parallel method to Wang but does not supply elements identified by the Examiner as missing in Wang.

For the reasons set forth above, it is applicant's contention that neither Wang nor Ronaghi, nor a combination thereof teaches or suggests the features of the present invention, as recited in claim 1 or claim 14.

As for the rejection of the retained dependent claims, these claims depend on claims 1 and 14, share its presumably allowable features, and therefore it is respectfully submitted that these claims should also be allowed.

Withdrawal of the rejection of claims 1-7 and 9-18 under 35 U.S.C. §103(a) and allowance thereof are thus respectfully requested.

REJECTION OF CLAIM 8 UNDER 35 U.S.C. §103(a) AS BEING UNPATENTABLE OVER WANG IN VIEW OF RONAGHI AND FURTHER IN VIEW OF STANTON.

The Examiner alleges that Wang and Ronaghi together teach the limitations of claim 8 but concedes that none of these references teach that the terminator nucleotides is capable of covalently cross linking the primer to the non-target nucleic acid. The Examiner's explanation is that Stanton teaches cross linking a desired allele to a complementary oligonucleotide by a cross linking agent thereby protecting the allele from degradation.

However, claim 8 and the specification in paragraph [053] and further claims a covalent cross linking of the primer to the non-target nucleic acid, while the Stanton reference describes in paragraph [0142] as cited by the Examiner that the cross linking is by chemical means to the target DNA. Two very different reactions and very different steps.

It is also applicant's contention that the Examiner relied upon hindsight to arrive at the determination of obviousness. It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *In re Gorman,* 933 F.2d 982. In the case at hand, there is no teaching or suggestion supporting the combination as proposed by the Examiner. The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 733 F.2d at 902.

Combining the Wang reference with Ronaghi and Stanton to supply the missing limitation amount to the afore-stated hindsight approach, where only when the invention is known can the specific limitations be found in other places and then combined.

For the reasons set forth above, it is applicant's contention that neither Wang nor Ronaghi, nor a combination thereof teaches or suggests the features of the present invention, as recited in claim 1 or claim 14.

Withdrawal of the rejection of claim 8 under 35 U.S.C. §103(a) and allowance thereof are thus respectfully requested.

CONCLUSION

Applicant believes that when reconsidering the claims in the light of the above comments, the Examiner will agree that the invention is in no way properly met or anticipated or even suggested by any of the references however they are considered.

None of the references discloses a method as set forth in claims 1 and 14.

In view of the above presented remarks and amendments, it is respectfully submitted that all claims on file should be considered patentably differentiated over the art and should be allowed.

Reconsideration and allowance of the present application are respectfully requested.

Should the Examiner consider necessary or desirable any formal changes anywhere in the specification, claims and/or drawing, then it is respectfully requested that such changes be made by Examiner's Amendment, if the Examiner feels this would facilitate passage of the case to issuance. If the Examiner feels that it might be helpful in advancing this case by calling the undersigned, applicant would greatly appreciate such a telephone interview.

Respectfully submitted,

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